Three-dimensional versus four-dimensional dose calculation for volumetric modulated arc therapy of hypofractionated treatments

Ehrbar, Stefanie ; Lang, Stephanie ; Stieb, Sonja ; Riesterer, Oliver ; Stark, Luisa Sabrina ; Guckenberger, Matthias ; Klöck, Stephan

Abstract: PURPOSE Respiratory motion is a non-negligible source of uncertainty in radiotherapy. A common approach is to delineate the target volume in all respiratory phases (ITV) and to calculate a treatment plan using the average reconstruction of the four-dimensional computed tomography (4DCT) scans. In this study the extent of the interplay effect caused by interaction between dynamic dose delivery and respiratory tumor motion, as well as other motion effects were investigated. These effects are often ignored when the ITV concept is used. METHODS AND MATERIALS Nine previously treated patients with in ten abdominal or thoracic cancer lesions (3 liver, 3 adrenal glands and 4 lung lesions) were selected for this planning study. For all patients, phase-sorted respiration-correlated 4DCT scans were taken, and volumetric modulated arc therapy (VMAT) treatments were planned using the ITV concept. Margins from ITV to planning target volume (PTV) of 3-10mm were used. Plans were optimized and dose distributions were calculated on the average reconstruction of the 4DCT. 4D dose distributions were calculated to evaluate motion effects, caused by the interference of dynamic treatment delivery with respiratory tumor motion and inhomogeneously planned target dose. These calculations were performed on the phase-sorted CT series with a respiration-correlated assignment of the treatment plan's monitor units (MU) to the respiration phases of the 4DCT. The 4D dose was accumulated with rigid as well as deformable registrations of the CT series and compared to the original 3D dose distribution. Maximum, minimum and mean doses to ITV and PTV, and maximum or mean doses to organs at risk (OAR), were compared after rigid accumulation. The dose variation in the gross tumor volume (GTV) was compared after deformable registration. RESULTS Using rigid registrations, variations in the investigated dose parameters between 3D and 4D dose calculations were found to be within -2.1% to 1.4% for all target volumes and within -0.8% to 1.7% in OAR. Using deformable registrations, dose differences in the GTV were below 3.8% for dose accumulation of lung and adrenal gland patients. For liver patients the used deformable registrations were not considered to be robust enough. It was also shown that a major part of the dose differences originates from the Hounsfield unit differences between 3D and 4D calculations, regardless of the interplay effect. CONCLUSION The evaluated motion effects during VMAT treatments resulted in negligible dose variability. Therefore, the approximation of calculating the dose on the average reconstruction of the 4DCT (3D dose calculation), instead of calculating on the respiration-correlated phase CTs (4D dose calculation) with assignment of the corresponding MUs, gives acceptable results.

DOI: https://doi.org/10.1016/j.zemedi.2015.06.010

Originally published at:
Ehrbar, Stefanie; Lang, Stephanie; Stieb, Sonja; Riesterer, Oliver; Stark, Luisa Sabrina; Guckenberger, Matthias; Klöck, Stephan (2016). Three-dimensional versus four-dimensional dose calculation for volumetric modulated arc therapy of hypofractionated treatments. Zeitschrift für medizinische Physik, 26(1):45-53.
DOI: https://doi.org/10.1016/j.zemedi.2015.06.010

Received Date: 16 January 2015
Accepted Date: 12 June 2015

Title page

Proposed journal: Zeitschrift für Medizinische Physik

Title: Three-dimensional versus four-dimensional dose calculation for volumetric modulated arc therapy of hypofractionated treatments

Titel: Unterschiede zwischen drei- und vierdimensionaler Dosisberechnung hypofraktionierter Behandlungen mit Volumen-modulierter Bogentherapie

Authors: Stefanie Ehrbar[1,3], Stephanie Lang[1], Sonja Stieb[1], Oliver Riesterer[1], Luisa Sabrina Stark[1], Matthias Guckenberger[1], Stephan Klöck[1]

[1] *Department of Radiation Oncology, University Hospital Zurich, Rämistrasse 100, 8091 Zürich, Switzerland*
[3] stefanie.ehrbar@usz.ch

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as
doi: 10.1016/j.zemedi.2015.06.010

Abstract

Purpose: Respiratory motion is a non-negligible source of uncertainty in radiotherapy. A common approach is to delineate the target volume in all respiratory phases (ITV) and to calculate a treatment plan using the average reconstruction of the four-dimensional computed tomography (4DCT) scans. In this study the extent of the interplay effect caused by interaction between dynamic dose delivery and respiratory tumor motion, as well as other motion effects were investigated. These effects are often ignored when the ITV concept is used.

Methods and Materials: Nine previously treated patients with in ten abdominal or thoracic cancer lesions (3 liver, 3 adrenal glands and 4 lung lesions) were selected for this planning study. For all patients, phase-sorted respiration-correlated 4DCT scans were taken, and volumetric modulated arc therapy (VMAT) treatments were planned using the ITV concept. Margins from ITV to planning target volume (PTV) of 3-10 mm were used. Plans were optimized and dose distributions were calculated on the average reconstruction of the 4DCT. 4D dose distributions were calculated to evaluate motion effects, caused by the interference of dynamic treatment delivery with respiratory tumor motion and inhomogeneously planned target dose. These calculations were performed on the phase-sorted CT series with a respiration-correlated assignment of the treatment plan's monitor units (MU) to the respiration phases of the 4DCT. The 4D dose was accumulated with rigid as well as deformable registrations of the CT series and compared to the original 3D dose distribution. Maximum, minimum and mean doses to ITV and PTV, and maximum or mean doses to organs at risk (OAR), were compared after rigid accumulation. The dose variation in the gross tumor volume (GTV) was compared after deformable registration.

Results: Using rigid registrations, variations in the investigated dose parameters between 3D and 4D dose calculations were found to be within -2.1% to 1.4% for all target volumes and within -0.8% to 1.7% in OAR. Using deformable registrations, dose differences in the GTV were below 3.8% for dose accumulation of lung and adrenal gland patients. For liver patients the used deformable registrations were not considered to be robust enough. It was also shown that a major part of the dose differences originates from the Hounsfield unit differences between 3D and 4D calculations, regardless of the interplay effect.

Conclusion: The evaluated motion effects during VMAT treatments resulted in negligible dose variability. Therefore, the approximation of calculating the dose on the average reconstruction of the 4DCT (3D dose calculation), instead of calculating on the respiration-correlated phase CTs (4D dose calculation) with assignment of the corresponding MUs, gives acceptable results.

Keywords: VMAT, Respiratory motion, Interplay effect, SBRT

Zusammenfassung

Hintergrund: Die Atembewegung ist eine nicht zu vernachlässigende Fehlerquelle in der Strahlentherapie. Ein gebräuchlicher Ansatz ist es, das Zielvolumen in allen Atemphasen zu konturieren (ITV) und den Bestrahlungsplan auf der gemittelten Rekonstruktion der vier-dimensionalen Computertomographie Aufnahme (4DCT) zu berechnen. Diese Studie untersucht den Interaktions-Effekt (Interplay), welcher durch die Wechselwirkung zwischen der dynamischen Bestrahlung und der atembedingten Tumorbewegung zustande kommt, und andere Bewegungseffekte. Diese Effekte werden oft nicht berücksichtigt, wenn das ITV-Konzept verwendet wird.
Methoden und Materialien: Neun vorgängig behandelte Patienten mit insgesamt zehn abdominalen oder thorakalen Tumorläsionen (3 Leber-, 3 Nebennieren- und 4 Lungentumoren) wurden für diese Planungsstudie ausgewählt. Für alle Patienten wurden phasensortierte, atemkorrelierte 4DCTs aufgenommen und Behandlungspläne für volumenmodulierte Bogenbestrahlung (VMAT) nach dem ITV-Konzept erstellt mit ITV-Expansionen von 3-10 mm zur Erstellung des Planungszielvolumens (PTV). Die Pläne wurden optimiert und die Dosisverteilungen auf der gemittelten Rekonstruktion des 4DCT berechnet. 4D-Dosisverteilungen wurden zur Auswertung der Bewegungseffekte berechnet, die durch die Interaktion der dynamischen Bestrahlung mit der respiratorischen Tumorbewegung und inhomogen geplanter Dosis im Zielvolumen verursacht sind. Dazu wurden Dosisberechnungen auf Phasen-sortierten CT Serien mit atemkorrelierter Zuteilung der Monitoreinheiten (MU) des Behandlungsplanes zu den Atemphasen des 4DCT durchgeführt. Die 4D-Dosis wurde akkumuliert nach rigider sowie auch nach deformierbarer Registrierung der CT Serien und mit der originalen 3D-Dosisverteilung verglichen. Die maximale, minimale und gemittelte Dosis im ITV und PTV und die maximale oder gemittelte Dosis in Risikoorganen (OAR) wurden im Falle rigider Registrierung verglichen und die Dosis zum Tumorvolumen (GTV) nach deformierbarer Registrierung.
Resultate: Der Vergleich von 3D- und 4D-Berechnungen unter Verwendung rigider Registrierung ergab Differenzen in den untersuchten Dosisparameter von -2.1 bis 1.4% für alle Zielvolumina und von -0.8 bis 1.7% für OARs. Bei den deformierbaren Registrierungen waren die Dosisdifferenzen im GTV für Lungen- und Nebennierenläsionen unter 3.8%. Im Falle der Leberläsionen erwies sich die deformierbare Registrierung als nicht robust genug. Es wurde ebenfalls gezeigt, dass ein grosser Anteil der gefundenen Dosisunterschiede durch die unterschiedlichen Hounsfield-Einheiten der 3D- und 4D-Berechnungen herrühren, unabhängig vom Interaktions-Effekt.
Zusammenfassung: Die Auswertung der Bewegungseffekte während VMAT-Behandlungen zeigte eine vernachlässigbare Dosisvariabilität. Daher liefert die Näherung, die Dosis auf der gemittelten Rekonstruktion des 4DCT (3D Dosisberechnung) zu berechnen, anstelle der Berechnung auf den atemkorrelierten Phasen-CTs mit entsprechender MU-Zuteilung, akzeptable Resultate.

Schlüsselwörter: VMAT, Atembewegung, Interplay-Effekt, SBRT

Introduction

Respiration induced internal organ and tumor motion is a non-negligible source of uncertainty in radiotherapy and has been studied by several authors. Motion of thoracic and abdominal organs or tumors was found to be most prominent in superior-inferior (SI) direction. Motion amplitudes up to 34 mm were found for liver tumors [1], 35 mm for lung tumors [2], and 27 mm for lesions in adrenal glands [3]. Respiratory motion affects the dose to the tumor in two ways: the gradient effect (motion blur) and the interplay effect [4]. Neglecting the tumor motion in treatment planning would lead to an underdosage at the edges of the moving target volume, the so called gradient or blurring effect. To prevent underdosage of the tumor, the internal target volume (ITV) concept is used as a common treatment approach [5]: A motion-encompassing delineation of the target volume defines the ITV and is constructed using respiration-correlated four-dimensional (4D) computed tomography (CT). The ITV concept ensures dose coverage of the tumor volume over the complete treatment session under free breathing, and prevents dose blurring at the tumor edges, as long as the dose is planned homogeneously. Since stereotactic body radiotherapy (SBRT) is often planned with inhomogeneous target dose the ITV concept is not fully capable to prevent dose blur. The tumor accumulates dose depending on its motion pattern through the high and low dose regions within the ITV. This is a pure spatial effect. If the beam itself moves or changes in size, temporal effects additionally alter the target dose. The interplay between beam alterations and tumor motion can lead to inhomogeneities in dose to the moving regions and partial target miss [4].

Rietzel et al. [6] and Starkshall et al. [7] performed 4D treatment planning studies, investigating the impact of tumor motion on the dose distribution during intensity modulated radiotherapy (IMRT) treatments. They found dose perturbations of up to 2% and 5%, respectively, in the target volume but neglected temporal components in their calculations. For fixed-field IMRT the interplay effect between the multileaf collimator (MLC) and tumor motion was investigated by several authors [8], [9], [10]. Jiang et al. [9] found the interplay of fixed-field IMRT to reach 18% dose difference for one fraction delivered with five fields, but to average out (1-2%) over 30 fractions. In stereotactic body radiotherapy (SBRT) the dose is delivered in only a few high-dose fractions and the dose averaging might be less pronounced than with conventional fractionation. Recent studies showed a negligible amount of interplay effect for lung SBRT during IMRT and VMAT treatments. Rao et al. [11] showed dose differences around 1% in the target. They included temporal effects, but without separating the contributions from different motion effects. Ong et al. [12] showed with film dosimetry that the motion effects on the delivered dose for RapidArc (Varian Medical Systems, USA) lung SBRT are not significant, if the irradiation is delivered in two or more arcs. Stambaugh et al. [13] used motion perturbation methods to reconstruct measured phantom dose received by a moving tumor. They were able to separate the interplay from the blurring effect and found nearly no impact of the interplay on the near-minimum dose in the target. Zou et al. [14] showed less than 1.5% change in PTV dose coverage using 4D dose calculations for lung SBRT using VMAT.

With the ITV concept, which is often used in clinical practice, only the dose blurring at the tumor edges is accounted for, while the possible impact of the interplay effect and the inhomogeneously planned dose of SBRT treatments within the ITV are neglected in treatment planning. Therefore we conducted a 4DCT planning study to investigate the extent of different motion effects on the dose distribution caused by dynamic dose delivery of VMAT treatments and respiratory tumor motion for inhomogeneous SBRT treatment plans. Original treatment plans that were calculated and optimized on the averaged reconstruction of the 4DCT image set, were compared to 4D dose calculation based on the phase-sorted respiration-correlated 4DCT image sets using rigid and deformable dose accumulations. The methods used in this study allowed for a separate investigation of the temporal and spatial motion effects, and the dose variations caused by alternation in Hounsfield units (due to positional changes of the tumor during respiration) between the 3D and 4DCT.

Materials and Methods

Treatment planning

Nine patients with a total of ten cancer lesions (3 liver, 3 adrenal glands and 4 lung lesions) were selected for this retrospective 4D-planning study. For all patients phase-sorted, 4DCT scans were obtained under free breathing with the SOMATOM Definition AS Open (Siemens AG, Germany) CT scanner, and the respiration patterns were recorded using the real-time position management system RPM (Varian Medical Systems, USA). Using the recorded respiration pattern, 10 phase-sorted CT series (phase CTs) and the average of the 4DCT were reconstructed. The GTVs were segmented on all phase CTs. The ITV enclosing these GTVs was delineated on the average CT. Margins of 3 to 10 mm were added to the ITV in order to construct the PTV. Treatment plans were created for VMAT with 95% of the PTV receiving the prescribed dose, and a prescription isodose between 60% and 90%. This led to maximum inhomogeneities between 120% and 144%. The VMAT plans were optimized and calculated on the average reconstruction of the 4DCT data set using the treatment planning system Eclipse (Varian Medical System, USA), with the analytical anisotropic algorithm (AAA 11.0.31) as a dose calculation model. This dose distribution was called the 3D dose distribution. Patient characteristics and treatment details such as dose prescription, number of arcs, modulation degree, size of ITV and PTV, ITV-to-PTV margins, the 3D extent of tumor motion and the respiratory period are summarized in Tab. 1. The modulation degree is a measure of the treatment plan's complexity and modulation. We chose $MD = \sum_s (A_{T,s} * MU_s) / \sum_s (A_{MLC,s} * MU_s)$ to report on modulation, where $A_{T,s}$ is the target area from a certain segment's point of view, $A_{MLC,s}$ its MLC opening and MU_s the monitor units delivered in this segment. This measure yields a value higher or equal to 1, where 1 is the case of no modulation. The tumor motion was determined in the 4DCT data set, by calculating the maximal 3D displacement of the center of gravity (COG) position for the GTV in the different respiration phases. The COG position was determined with an in house developed C++ program based on the Insight Toolkit and the Visualization Toolkit (Kitware Inc., USA). The respiratory periods were obtained by averaging the periods of the patient specific respiration curves, provided by the RPM measurement taken during the 4DCT image acquisition.

For the evaluation of different motion effects, four-dimensional dose calculations were performed with and without the temporal effects taken into account.

4D dose calculation without interplay

For the 4D dose calculation by taking tumor motion into account, but neglecting temporal effects, the monitor units (MU) of every arc segment had to be distributed uniformly to the ten breathing phases. The original plans were re-calculated on the ten different phase-correlated CT series, each with 10% of the MUs from the original plan applied.

4D dose calculation with interplay

For the investigation of the interplay effect, the MUs of the original plan had to be chronologically assigned to the dedicated respiration phases (Figure 1). Therefore a phase-specific sub-plan was generated for each respiratory phase. The arcs of the VMAT plan were segmented into control points (CP) with a determined gantry position, dose rate, and MLC shape. All CPs lying in the time sections of the same respiration phase contribute dose to this phase and were considered in a phase specific sub plan. For all other CPs, not contributing dose to that respiratory phase, the dose rate was manually set to zero in the corresponding sub plan. No changes were made to the other plan parameters. The ten phase specific VMAT plans were applied to the corresponding phases in the 4DCT data set, and the dose distributions were calculated.

For the assignment of the control points to the respiratory phases, assumptions on the respiratory cycles were made. From the RPM measurements, the patients showed irregular respiratory patterns with mean periods from 2.6 to 5.7 s. For this study, steady respiratory cycles of 3.4 s were assumed for all patients. In our treatment system, 3.4 s is the delivery duration of 10 CP, leading to exactly 1 CP per

respiratory phase. These assumptions facilitated the assignment process, in order to avoid dividing the MUs of one CP over multiple phases.

Dose accumulation

To calculate the composite doses from the dose distribution on the ten phase CT series, rigid and deformable dose accumulations were performed.

Rigid dose accumulations were performed in Eclipse. Dose variations from 3D to 4D calculations in static structures such as PTV, ITV, and OARs that were delineated on the average reconstruction of the 4DCT could be evaluated. Dose parameters as maximum, minimum, and mean dose were investigated for ITV and PTV, mean or maximum (spinal cord, ribs) for OARs. The volume of the PTVs receiving 100% of the prescribed dose (V_{100}) was assessed from the dose-volume histograms. The 4D doses with rigid accumulations were also calculated with a slower respiratory period of 6.8 s with 2 CP per phase. In order to evaluate the dose variations to the moving GTV, 4D dose accumulations were performed with MIM Maestro (MIM Software Inc., USA). The built-in 4D dose accumulation tool of the software was used, which performs deformable registrations from all phase CTs against one chosen reference phase CT. Dose accumulations were performed against the end-of-exhale phase (50%) since it is the most stable, and against the 10% phase for comparison purposes. The accumulated 4D doses to the GTV delineated on the 10% and 50% phases were compared to the 3D doses to the GTV. The GTV dose values of the 3D calculations were estimated by averaging the minimum, maximum and mean dose values of the 10 drawn GTVs from the ten different respiration phases using the 3D dose distribution.

Dependence on beam-on timing

In the above mentioned 4D calculations, the assignment of the CPs to the phases, started with the 10% phase of the respiration cycle for all patients. To investigate the dependence of the interplay effect on the beam-on timing, meaning the concurrence of the switching-on of the beam with a specific respiration phase, the 4D dose distributions were calculated for patient 9 (lung lesion), with 10 different beam-on timings (starting at each of the 10 different respiration phases).

Comparisons

With and without the temporal splitting of the plans for the 4D dose calculation, and by using rigid and deformable registrations for dose accumulation, four distinct dose distributions can be calculated for every patient and compared against the original 3D distribution or against each other. Depending on the chosen dose calculations for comparison, four motion effects can be evaluated separately (summarized in Tab. 2):

1) The dose difference caused by the alternation of Hounsfield units between the 3DCT (average reconstruction of the 4DCT) and 4DCT (phase CTs)
2) The spatial dose accumulation effect due to inhomogeneous target dose
3) The temporal interplay effect on the dose distribution of static volumes (PTV, ITV)
4) The temporal interplay effect on the dose distribution of moving volumes (GTV).

Comparing 4D dose distributions with temporal components to the distributions without temporal components, should therefore only deliver the dose variation in a moving target caused by the interplay effect. The Wilcoxon signed rank test was used to compare the calculations. A p-value of less than 0.05 was considered as significant.

Spearman rank correlations with Bonferroni corrections for multiple testing were used to compare the modulation degree with the changes in PTV and ITV dose parameters.

Results

4D dose with rigid registrations

Three 4D calculations were performed: one without interplay and two with interplay (with fast or slow respiratory period). The 4D dose was accumulated on the average reconstruction using rigid registrations and compared to the 3D dose (Figure 2). The relative dose differences from 3D to 4D calculations were small, within ±2.1%, but significant.

The dose variations caused only by interplay effect, comparing 4D with against 4D without interplay, were significantly smaller than the variations from the 3D to 4D comparison.

This indicates that the obtained dose variations between 3D and 4D calculations are mainly caused by the change of Hounsfield units between the 3DCT and 4DCT, and not by the interplay effect itself. No significant correlations between the dose differences and extent of tumor motion, modulation degree, or treatment site were found.

4D dose with deformable registrations

Due to the lack of visible structures in the liver that are required for deformable registrations, these patients were excluded from the analysis with deformable dose accumulation.

In Figure 3, the results from the dose accumulation performed with deformable registrations are shown. The accumulations were performed twice, once with registering against and accumulating on the 10%-phase CT, and once against the 50%-phase CT as a reference CT. The comparison of 3D to 4D dose calculation showed dose variations of ±3.0%. Values up to 3.8% were found by comparing 4D dose calculations with and without interplay against each other, giving the pure temporal effects of the tumor motion.

Different values between accumulations against 10% and 50% phases were observed, especially in the minimum dose to the GTV. Differences up to 2.8% were found, while the GTV maximum dose did not change much.

Dependence on beam-on timing

The dose differences for the ten calculations with different beam-on timings are shown in Figure 4a. 4D calculations with fast respiratory cycle were investigated. A maximal dose spread over the ten calculations of 0.2% was found in the spinal cord. Comparing the 4D dose calculation with interplay effect against the 4D calculation without showed that all dose differences were in the range of ±0.1%. This is the amount of dose difference caused by temporal effects.

The influence of beam-on timing on the dose variations to the moving GTV was also investigated for the 4D dose accumulations after deformable registrations against the 10%-phase CT. The dose differences of the 4D calculations, compared to 3D and 4D without interplay, are shown in Figure 4b. The differences in the mean dose to the GTV was well compensated by the 4D dose difference without regarding interplay, but the differences in the minimum and maximum dose ranged from -1.2% to 1.1% over the ten beam-on timings.

Discussion

VMAT treatment planning for lung, liver, and adrenal gland lesions is often performed on the average reconstruction of the 4DCT. However, this is an approximation of the dose delivered in the different breathing phases. The dose to a moving target depends on different motion effects. The dose difference caused by alternation in Hounsfield units between the 3DCT and 4DCT, the spatial dose accumulation effect due to inhomogeneous target dose, and the temporal interplay effect on the dose distribution of static volumes (PTV, ITV) or moving volumes (GTV).

This study shows how 4D dose calculations can be performed to separately investigate these motion effects (Tab. 2). For the static ITV and PTV the overall dose variations caused by tumor motion were found to be small (±2%) and mainly caused by the alternation in Hounsfield units, while the temporal effect (interplay) showed minor impact on the dose distribution. Higher dose variations (up to 3.0%)

were found in the moving GTV, calculated with deformable registrations for adrenal gland and lung patients, than for the static volumes under rigid dose accumulations. Especially higher contributions from temporal effects (up to 3.8%) were found.

The small amount of dose difference found in this study is consistent with the results from the 4D planning studies performed by Rao et al. [11] and Zou et al. [14], as well as the phantom studies by Ong et al. [12] and Stambaugh et al. [13]. However it is in disagreement with the study published by Jiang et al. [9], which showed dose differences up to 18% to the target using a 5-field IMRT treatment technique. The high variation was measured near the tumor edge, where dose blurring is more pronounced. They did not use an ITV approach for blurring compensation, which explains the high dose difference. All investigated treatment plans included two or more arcs as proposed by Ong et al. Dose delivery with multiple arcs might act as a form of repainting the treatment volume in different respiratory phases, and thereby reducing dose inhomogeneities.

Another way to reduce interplay might be the use of breath hold or gating methods, keeping the tumor in a 'non-moving' position whilst the treatment is delivered. But it has to be considered that those techniques require advanced technology and prolong the treatment time.

Different dosimetric parameters (maximum, minimum, mean doses to predefined volumes) were evaluated in this work. These values are not bound to a spatial location within the examined volume. Therefore one could also be interested in γ-analyses of the dose distributions, but since the changes in minimum and maximum dose values are found to be small, this evaluation is assumed to show small variations as well. The evaluation of motion effects on the dose distribution was performed for the delivery of one single fraction only, and did not consider any fractionation, which could further reduce the dose differences caused by the interplay effect. The evaluation was also performed with only one specific beam-on timing. This could have an effect on the results, since the amount of interplay effect depends on the beam-on timing for the deformable dose accumulations as shown in Figure 4.

The literature shows bigger discrepancies in the liver than in the lung using deformable image registration [15], [16] due to the lack of visible structures in the liver. Based on this, no deformable dose accumulations were performed for liver patients. The accumulations for the remaining patients were also found to result in different minimum and mean dose to the GTV for registrations against different reference phases (Fig. 3, right). The dose accumulations were performed against the 10% and 50% phases, which correspond to the beginning and end of exhalation phases, respectively. These phases were chosen, because they showed less motion artifacts than the mid-respiration phases and therefore represent the GTV outline more accurately. However, by using these phases, the tumor is located at its most extreme positions and deformable dose accumulations might be more inaccurate than using a mid-ventilation position. The accuracy and robustness of the deformable registrations during the 4D dose accumulations performed with MIM Maestro cannot be verified and adapted, neither during nor after the registration process. Additionally, the GTVs of the different reference phases vary in location, size and shape, which include a delineation error as well. This might have an influence on the dose accumulation. More investigations are needed to separate the amount of dose difference originating from the spatial motion effects from the contribution due to possible inaccuracies in the deformable registrations.

The differences between the accumulations against the different breathing phases showed dose variations to the same order of magnitude as the comparison of 3D and 4D calculated doses (Fig. 3), accumulated with deformable registrations. Therefore the inaccuracy of deformable registrations for dose accumulations is the limiting factor of this study and interferes with a robust separation of the dose differences according to the different motion effects. Nevertheless, the overall dose differences were found to be small and probably not clinically relevant.

Another limitation of the study is the assumption of a constant respiratory period of 3.4 or 6.8 s, instead of using patient specific breathing cycles. This was done for easier handling of the assignment of CPs to the respiration phases. However, the dose differences between 3.4s and 6.8s were small, and therefore a more adequate assignment of the MU to the phases would be expected to show dose differences in the same range.

Conclusion

In this work a planning study was performed to investigate the difference in the dose distribution between 3D planning on the average CT, and 4D planning for VMAT treatments of moving abdominal and thoracic cancer lesions, planned with inhomogeneous target dose. Two different approaches for dose accumulation, rigid and deformable registrations, were studied.
Negligible dose variability was found. Therefore, the approximation of calculating the dose on the average reconstruction of the 4DCT (3D dose calculation), instead of on the respiration-correlated phase CTs with the assignment of the corresponding MUs, gives acceptable results.

Acknowledgements

This work was support by the grant CR32I3_153491 of the Swiss National Science Foundation.

Autors contribution

All authors read the manuscript carefully and approved it.

References

[1] Kirilova A, Lockwood G, Choi P, Bana N, Haider MA, Brock KK, Eccles C and Dawson LA. Three-dimensional motion of liver tumors using cine-magnetic resonance imaging. International Journal of Radiation Oncology*Biology*Physics. 2008; 71(4): 1189-95.

[2] Erridge SC, Seppenwoolde Y, Muller SH, van Herk M, De Jaeger K, Berlderbos JS, Boersma LJand Lebesque JV. Portal imaging to assess set-up errors, tumor motion and tumor shrinkage during conformal radiotherapy of non-small cell lung cancer. Radiotherapy and Oncology. 2003; 66(1): 79-85.

[3] Katho N, Onimaru R, Sakuhara Y, Abo D, Shimizu S, Taguchi H, Watanabe Y, Shinohara N, Ishikawa M and Shirato H. Real-time tumor-tracking radiotherapy for adrenal tumors. Radiotherapy and Oncology. 2008; 87(3): 418-24.

[4] Bortfeld T, Jiang S and Rietzel E. Effects of motion on the total dose distribution. Seminars in radiation oncology, Elsevier. 2004; 14: 41.

[5] Admiraal MA, Schuring D and Hurkmans CW. Dose calculations accounting for breathing motion in stereotactic lung radiotherapy based on 4D-CT and the internla target volume. Radiotherapy and Oncology. 2008; 86(1): 55-60.

[6] Rietzel E, Chen GTY, Choi NC and Willet CG. Four-dimensional image-based treatment planning: Target volume segmentation and dose calculation in the presence of respiratory motion. International Journal of Radiation Oncology* Biology* Physics. 2005; 61: 1535-50.

[7] Starkshall G, Britton K, McAleer MF, Jeter MD, Kaus MR, Bzdusek K, Mohan R and Cox JD. Potential dosimetric benefits of four-dimensional radiation treatment planning. International Journal of Radiation Oncology* Biology* and Physics*. 2005; 73: 1560-65.

[8] Chui CS, Yorke E and Hong L. The effects of intra-fraction organ motion on the delivery of intensity-modulated field with a multileaf collimator. Medical physics. 2003; 30(7): 1736-46.

[9] Jiang SB, Pope C, Al Jarrah KM, Kung JH, Bortfeld T and Chen GT. An experimental investigation on intra-fractional organ motion effects in lung IMRT treatments. Physics in medicine and biology. 2003; 48(12): 1773.

[10] Bortfeld T, Jokivarsi K, Goitein M, Kung J and Jiang SB. Effects of intra-fraction motion on IMRT dose delivery: statistical analysis and simulation. Physics in medicine and biology. 2002; 47(13): 2203.

[11] Rao M, Wu J, Cao D, Wong T, Mehta V, Shepard D and Ye J. Dosimetric impact of breathing motion in lung stereotactic body radiotherapy treatment using image-modulated radiotherapy and volumetric modulated arc therapy. International Journal of Radiation Oncology* Biology* Physics. 2012; 83(2): e251-56.

[12] Ong C, Verbakel WF, Cuijpers JP, Slotman BJ and Senan S. Dosimetric impact of interplay effect on RapidArc lung stereotactic treatment delivery. International Journal of Radiation Oncology* Biology* Physics. 2011; 79(1): 305-11.

[13] Stambaugh C, Nelms BE, Dilling T, Stevens C, Latifi K, Hang G, Moros E and Feygelman V. Experimentally studied dynamic dose interplay does not meaningfully affect target dose in VMAT SBRT lung treatments. Medical physics. 2013; 40(9): 091710.

[14] Zou W, Yin L, Shen J, Corradetti MN, Kirk M, Munbodh R, Fang P, Jabbour SK, Simone CB, Yue NJ, Rengan R and Teo BK. Dynamic simulation of motion effects in IMAT lung SBRT. Radiation Oncology. 2014; 9(1): 225.

[15] Brock KK and Deformable Registration Accuracy Consortium. Results of a multi-institution deformable registration accuracy study (MIDRAS). International Journal of Radiation Oncology* Biology* Physics. 2010; 76(2): 583-96.

[16] Liu F, Hu Y, Zhang Q, Kincaid R, Goodman KA and Mageras GS. Evaluation of deformable image registration and a motion model in CT images with limited features. Physics in medicine and biology. 2012; 57(9): 2539.

Tables

Table 1: Summary of patient characteristics: Tumor location, dose prescription, number of treated arcs, modulation degree, ITV and PTV size, ITV-to-PTV margin, motion amplitude and mean respiratory period.

Patient	Dose Prescription	# Arcs	Modulation Degree	ITV Volume (cm^3)	PTV Volume (cm^3)	Margin (mm)	Motion (mm)	Respiratory Period (s)
Liver								
1	5 x 8.5 Gy = 42.5 Gy	2	3.9	44.8	112.8	6	34	4.7
2	4 x 12 Gy = 48 Gy	3	1.9	37.7	85.8	6	14	2.6
3	10 x 5 Gy = 50 Gy	2	1.8	49.0	106.0	6	10	3.3
Adrenal glands								
4	3 x 10 Gy = 30 Gy	2	1.6	29.7	49.1	3	9	4.1
5	5 x 7 Gy = 35 Gy	3	2.9	36.1	153.9	10	21	5.7
6	10 x 5 Gy = 50 Gy	2	1.4	28.4	66.2	5	7	3.0
Lung								
7	5 x 9 Gy = 45 Gy	3	2.5	13.0	38.9	6	10	4.8
8	5 x 6.5 Gy = 32.5 Gy	2	1.9	73.6	148.2	6	8	4.8
9	8 x 7.5 Gy = 60 Gy	4	1.4	94.6	161.1	5	6	3.0
10	3 x 12.5 Gy = 37.5 Gy	4	2.1	9.2	25.5	5	9	3.7

Table 2: Choice of the two compared calculation methods determines the investigated motion effect. The dose difference between two dose calculations (3D or 4D, with or without interplay, rigid or deformable registrations) can be caused by: Density (Hounsfield unit) differences (HU) between the 3D and 4DCTs, the spatial effect (Spatial) on dose accumulation caused by inhomogeneously planned ITV dose and the temporal effects (Temporal) due to interplay for static or moving (dynamic) volumes.

Without Interplay 4D rigid	*HU*		
With Interplay 4D rigid	*HU* *Temporal (static)*	*Temporal (static)*	
Without Interplay 4D deformable	*HU* *Spatial*	*Spatial*	
With Interplay 4D deformable	*HU* *Spatial* *Temporal (dynamic)*	*Spatial* *Temporal (dynamic)*	*Temporal (dynamic)*
	3D original	**Without Interplay 4D rigid**	**Without Interplay 4D deformable**

Figures

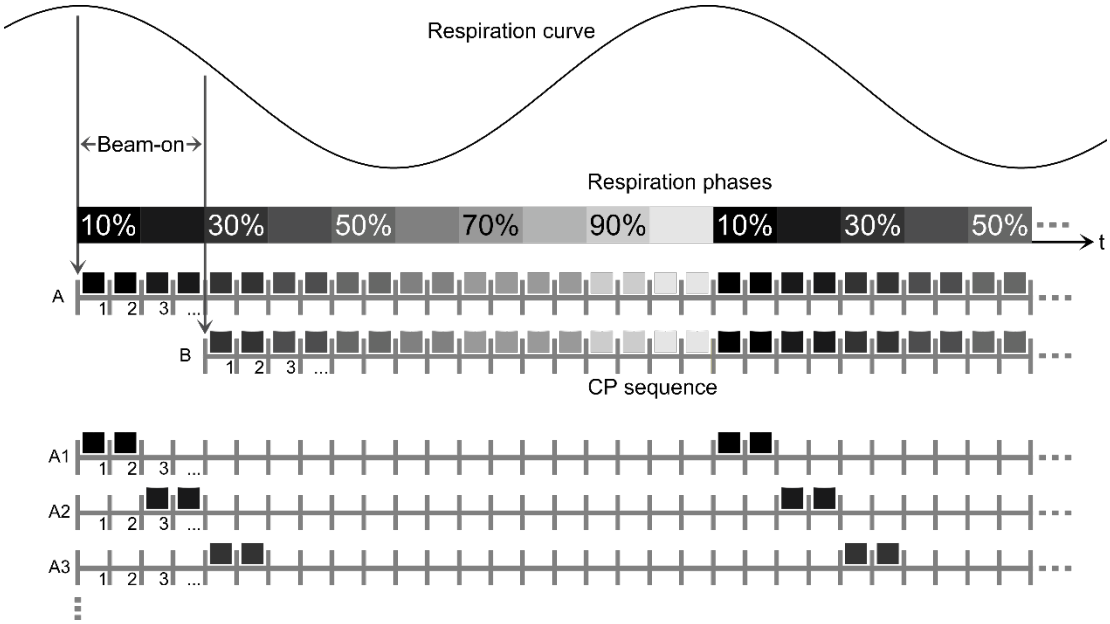

Fig. 1: Assignment of control points: The respiration curve is divided into 10 equally long phases. The different control points (squares in the CP sequence) were assigned to the respiration phases. A: Beam-on timing coincides with 10% phase. B: Beam-on with 30% phase. A1, A2, A3: CP sequence of a particular sub plan only delivering dose to the corresponding respiration phase.

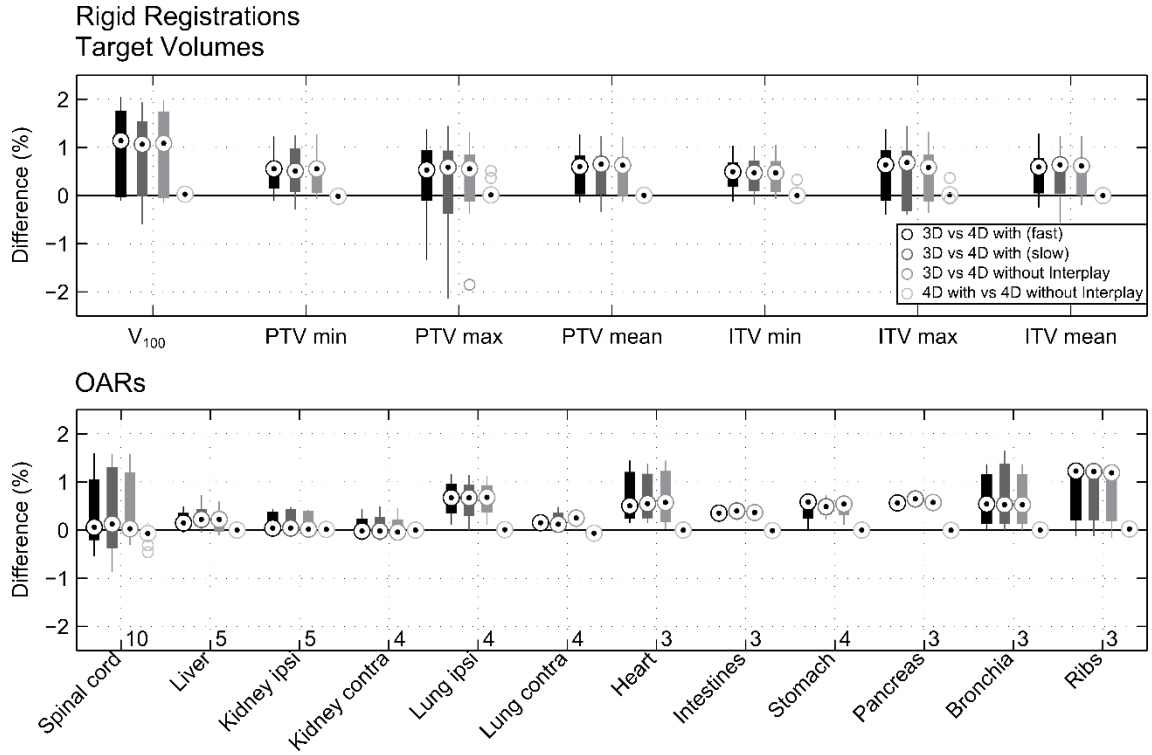

Fig. 2: After rigid registrations: Boxplots of relative dose variations of the 10 lesions for dose parameters (minimum, maximum or mean dose) of ITV, PTV and OARs. Box edges cover the 25% and 75% quantiles and whiskers exceed up to maximal 1.5 times the box width on both sides. Outliers are marked with circles. Comparisons of original 3D dose calculations to 4D calculations with interplay under fast respiration (black), to 4D with interplay under slow respiration (dark gray) and to 4D without interplay (gray) and between the 4D calculations with and without interplay (light gray) are shown, with rigid registrations used for dose accumulation. Contra = contralateral, ipsi= ipsilateral. Numbers give the number of patient with this OAR.

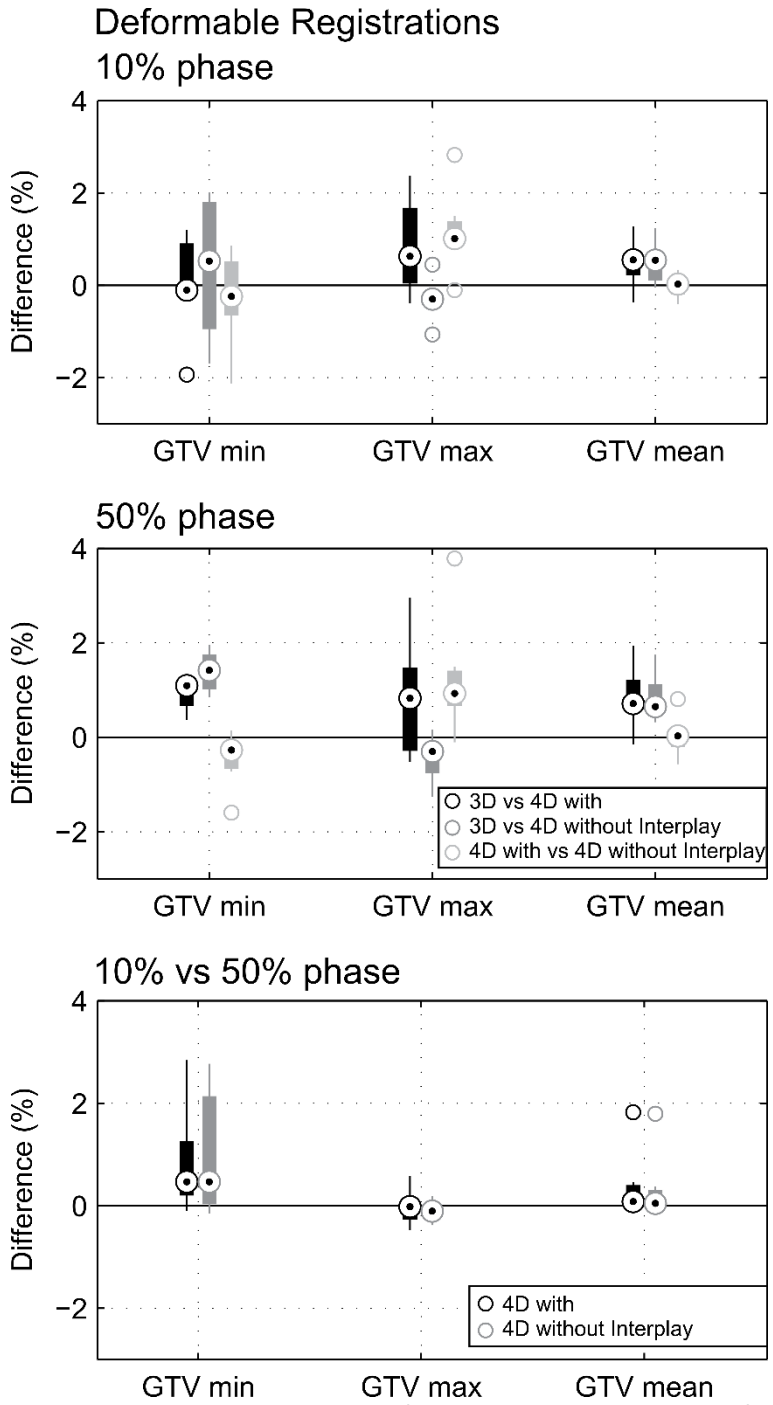

Fig. 3: After deformable registrations: Boxplots of relative dose variations of the 7 lesions dose parameters (minimum, maximum and mean dose) of the GTV. Comparisons of original 3D dose calculations to 4D calculations with interplay (black) and to 4D without interplay (gray) and between the 4D calculations with and without interplay (light gray) are shown, with deformable registrations against the 10% (top) and the 50% phase (middle) for dose accumulation. Differences between the two dose accumulations on the 10% and 50% phases are shown (bottom).

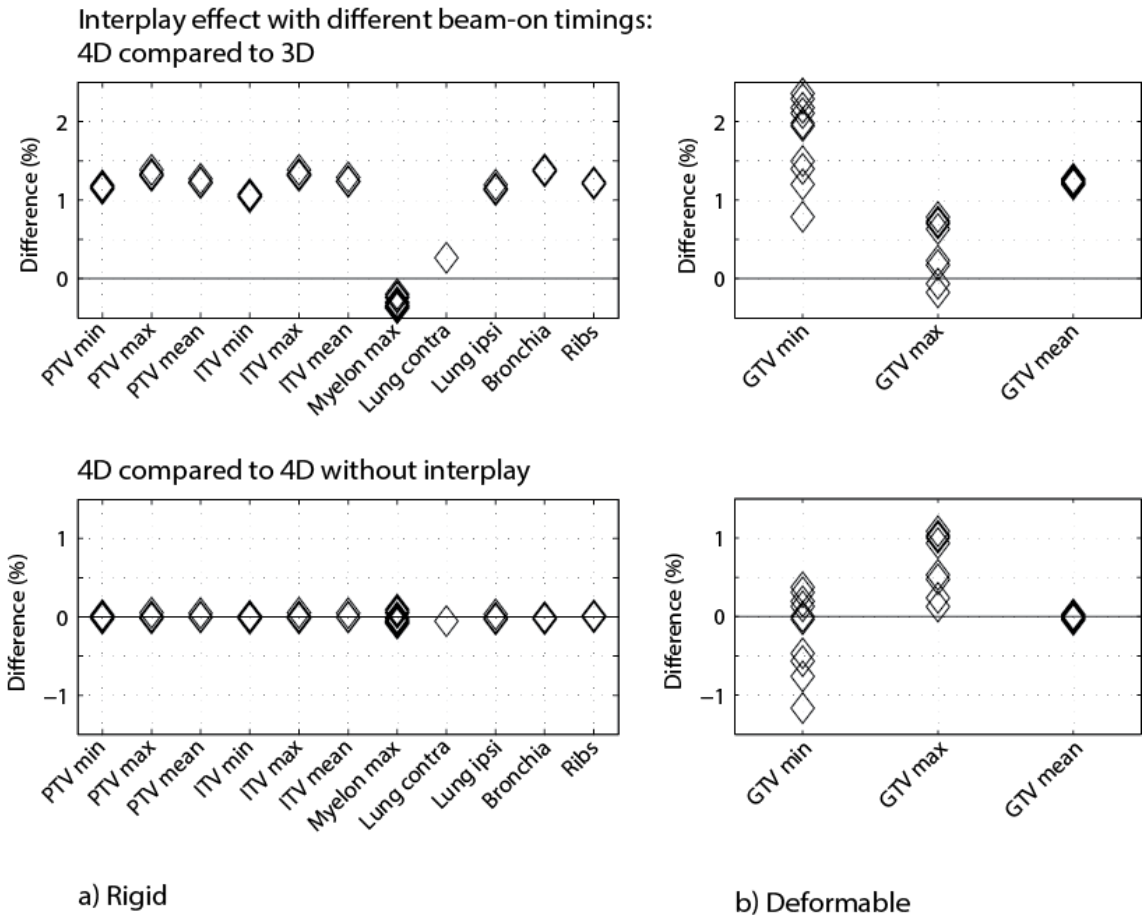

Fig. 4: Influence of beam-on timing for one patient with a lung lesion: Top: Dose differences between 4D dose calculations with interplay compared to 3D dose calculations considering 10 different beam-on timings. Bottom: Dose differences between 4D dose calculations with and without interplay using a) rigid or b) deformable registrations for dose accumulation.